

Claims

1. Oligonucleotides having a sequence at least 80% identical to a sub-sequence of SEQ ID NO 1 or SEQ ID NO 2 or SEQ ID NO 94 or SEQ ID NO 95 or SEQ ID NO 96 comprising 8 to 50 nucleobases, wherein said sequence is capable of hybridizing sufficiently with the region encompassing the translation initiation or termination codon of the open reading frame of the gene encoding TGF-R or TGF-R_{II}, or a region of the mRNA encoding TGF-R or TGF-R_{II} which is a "loop" or "bulge" and which is not part of a secondary structure and mimetics, variants, salts and optical isomers of said sequence.
2. Oligonucleotides having a sub-sequence of SEQ ID NO 1 or SEQ ID NO 2 or SEQ ID NO 94 or SEQ ID NO 95 or SEQ ID NO 96 comprising 8 to 50 nucleobases and mimetics, variants, salts and optical isomers thereof.
3. Oligonucleotides according to claim 2, selected from the group comprising SEQ ID NO 3 to SEQ ID NO 93.
4. Oligonucleotides according to claim 3 selected from the group comprising:
 - SEQ ID NO 3: 5'-CAGCCCCCGACCCATG-3'
 - SEQ ID NO 33: 5'-CAGCCCCCGACCCATGGCAG-3'
 - SEQ ID NO 34: 5'-CAGCCCCCGACCCATGGCA-3'
 - SEQ ID NO 35: 5'-CAGCCCCCGACCCATGGC-3'
 - SEQ ID NO 36: 5'-CAGCCCCCGACCCATGG-3'
 - SEQ ID NO 41: 5'-GCAGCCCCCGACCCATGGCA-3'
 - SEQ ID NO 42: 5'-GCAGCCCCCGACCCATGGC-3'
 - SEQ ID NO 43: 5'-GCAGCCCCCGACCCATGG-3'
 - SEQ ID NO 44: 5'-GCAGCCCCCGACCCATG-3'
 - SEQ ID NO 49: 5'-AGCAGCCCCCGACCCATGGC-3'
 - SEQ ID NO 50: 5'-AGCAGCCCCCGACCCATGG-3'
 - SEQ ID NO 51: 5'-AGCAGCCCCCGACCCATG-3'
 - SEQ ID NO 56: 5'-GAGCAGCCCCCGACCCATGG-3'
 - SEQ ID NO 57: 5'-GAGCAGCCCCCGACCCATG-3'
 - SEQ ID NO 62: 5'-TGAGCAGCCCCCGACCCATG-3'
 - SEQ ID NO 73: 5'-ATGTGAAGATGGGCAAGACC-3'
 - SEQ ID NO 74: 5'-ATCTCCATGTGAAGATGGGC-3'
 - SEQ ID NO 75: 5'-AACGGCCTATCTCGAGGAAT-3'
 - SEQ ID NO 76: 5'-AACATCGTCGAGCAATTTCC-3'
 - SEQ ID NO 77: 5'-AATCCAACCTCTTTGCCCTT-3'

SEQ ID NO 78: 5'-AAACCTGAGCCAGAACCTGA-3'
 SEQ ID NO 79: 5'-AGGGCGATCTAATGAAGGGT-3'
 SEQ ID NO 80: 5'-AGTGCACAGAAAGGACCCAC-3'
 SEQ ID NO 81: 5'-ACACTGGTCCAGCAATGACA-3'
 SEQ ID NO 82: 5'-TTCCTGTTGACTGAGTTGCG-3'
 SEQ ID NO 83: 5'-CACTCTGTGGTTTGGAGCAA-3'
 SEQ ID NO 84: 5'-CAAGGCCAGGTGATGACTTT-3'
 SEQ ID NO 85: 5'-CACACTGGTCCAGCAATGAC-3'
 SEQ ID NO 86: 5'-CTGACACCAACCAGAGCTGA-3'
 SEQ ID NO 87: 5'-CTCTGCCATCTGTTTGGGAT-3'
 SEQ ID NO 88: 5'-TCAAAAAGGGATCCATGCTC-3'
 SEQ ID NO 89: 5'-TGACACCAACCAGAGCTGAG-3'
 SEQ ID NO 90: 5'-TGATGCCTTCCTGTTGACTG-3'
 SEQ ID NO 91: 5'-TTCCTGTTGACTGAGTTGCG-3'
 SEQ ID NO 92: 5'-TTCTCCAAATCGACCTTTGC-3'
 SEQ ID NO 93: 5'-GGAGAGTTCAGGCAAAGCTG-3'

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5. Pharmaceutical preparation comprising at least one oligonucleotide according to any one of claims 1 – 4 as well as mimetics, variants, salts and optical isomers thereof and/or at least one antisense compound selected from the group comprising a vector allowing to transcribe an antisense oligonucleotide and/or at least one ribozyme, external guide sequence (EGS), oligozyme, and short catalytic RNA or catalytic oligonucleotide which hybridize to the target nucleic acid encoding TGF-R or TGF-R_{II} and inhibit its expression together with at least one pharmaceutically acceptable carrier, excipient or diluents.
6. Pharmaceutical preparation according to claim 5, wherein the pharmaceutical preparation is an infusion solution or a solid matrix for continuous release of the active ingredient.
7. Pharmaceutical preparation according to claim 5 or 6, wherein the pharmaceutical preparation is suitable for local administration into the brain.
8. Use of at least one oligonucleotide according to any one of claims 1 to 4 as well as mimetics and variants thereof and/or at least one antisense compound selected from the group comprising a vector allowing to transcribe an antisense oligonucleotide and/or at least one ribozyme, external guide sequence (EGS), oligozyme, and short catalytic RNA or catalytic oligonucleotide which hybridize to the target nucleic acid encoding TGF-R or TGF-R_{II} and inhibit its expression

or a pharmaceutical formulation according to any one of claim 5 to 7 for promoting successful regeneration and functional reconnection of damaged neural pathways.

- 5 9. Use of at least one oligonucleotide according to any one of claims 1 to 4 as well as mimetics and variants thereof and/or at least one antisense compound selected from the group comprising a vector allowing to transcribe an antisense oligonucleotide and/or at least one ribozyme, external guide sequence (EGS), oligozyme, and short catalytic RNA or catalytic oligonucleotide which hybridize
10 to the target nucleic acid encoding TGF-R or TGF-R_{II} and inhibit its expression or a pharmaceutical formulation according to any one of claim 5 to 7 for prophylaxis, therapeutic prevention and treatment of neurodegenerative, traumatic / posttraumatic, vascular/hypoxic, neuroinflammatory and postinfectious Central Nervous System disorders, as well as age induced
15 decreases in neuronal stem cell renewal.
10. Use according to claim 9 for inhibiting TGF-R and/or TGF-R_{II} expression in diseases associated with up-regulated or enhanced TGF-R and/or TGF-R_{II} levels.
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11. Use according to claim 9 or 10, wherein the diseases associated with up-regulated or enhanced TGF-R and/or TGF-R_{II} levels or the neurodegenerative disorders and neuroinflammatory disorders are selected from the group comprising: Alzheimer's diseases, Parkinson's disease, Creutzfeldt Jakob
25 disease (CJD), new variant of Creutzfeldt Jakobs disease (nvCJD), Hallervorden Spatz disease, Huntington's disease, Multisystem Atrophy, Dementia, Frontotemporal Dementia, or other Motor Neuron Disorders, Amyotrophic Lateral Sclerosis, Spinal Muscular Atrophy, Spinocerebellar Atrophies (SCAs), schizophrenia, affective disorders, major depression,
30 meningoencephalitis, bacterial meningoencephalitis, viral meningoencephalitis, CNS autoimmune disorders, Multiple Sclerosis (MS), acute ischemic / hypoxic lesions, stroke, CNS and spinal cord trauma, head and spinal trauma, arteriosclerosis, atherosclerosis, microangiopathic dementia, Binswanger' disease (Leukoaraiosis), retinal degeneration, cochlear degeneration, macular
35 degeneration, cochlear deafness, AIDS-related dementia, retinitis pigmentosa, fragile X-associated tremor/ataxia syndrome (FXTAS), progressive supranuclear palsy (PSP), striatonigral degeneration (SND), olivopontocerebellar degeneration (OPCD), Shy Drager syndrome (SDS), age dependant memory deficits, neurodevelopmental disorders associated with

dementia, Down's Syndrome, synucleinopathies, Superoxide Dismutase Mutations, Trinucleotide Repeat Disorders, trauma, hypoxia, vascular diseases, vascular inflammations, CNS-ageing

- 5 12. Method for identifying a compound interfering with (a) the biological activity of TGF-R and/or TGF-R_{II} or the expression of TGF-R and/or TGF-R_{II}, or (b) the TGF-β1/TGF-R signaling, comprising the steps of:
- 10 (a) incubating a candidate compound with a test system comprising TGF-β1 and neuronal precursor cells; and
- (b) assaying the expression of active TGF receptors or the proliferation of the neuronal precursor cells;
- wherein
- 15 (c) an abolition of (i) the suppression of expression of active TGF receptors or (ii) suppression of proliferation of the neuronal precursor cells compared to the test system in the absence of said test compound is indicative of the presence of a candidate compound having the desired properties.